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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,664	08/30/2001	David Botstein	P2548P1C8	2448

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,664	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-02

DETAILED ACTION

1. Claims 27-34 are pending in the instant application. Claim 33 has been amended and claims 25 and 26 been canceled as requested by Applicant in the Paper filed April 8, 2005.

Withdrawn Rejections

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 27-34 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 27-34 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The basis for these rejections is set forth at pp. 3-7 of previous Office Action (Paper

mailed March 24, 2003), at pp. 3-6 of Paper mailed Sept. 24, 2003, at pp. 3-14 of the Paper Mailed March 17, 2005, and below.

Applicant's arguments (pp. 4-11, Paper filed July 11, 2005) have been fully considered but are not found to be persuasive for the following reasons.

To review prosecution briefly, the Examiner has made a prima *facie case* that the mild amount of gene amplification (approximately 2 fold to 4 fold) of nucleic acids encoding the claimed protein are not indicative of an increased amount of protein.

Applicants traverse the rejections and assert that as the polypeptides are encoded by an amplified DNA sequence, the polypeptides have utility as diagnostic markers for determining the presence of tumor cells in lung and/or colon tissue samples. Applicants cite *In re Langer, In re Jolles, In re Irons and In re Sichert,* and submit that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 USC § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." Applicants also assert that the credibility of the asserted utility is to be assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record. Applicants also cite *In re Oetiker,* and submit that the evidentiary standard to be used throughout ex parte examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration, and thus to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.

Applicants discuss the Pollack, Orntoft, Hyman, Bermont, Varis and Hu references on

pages 5-6 of the response, and disagree with the Office that these are proper bases for rejecting Applicants' reliance on these references, and even assuming arguendo that Pollack, Hyman and Varis only teach correlation between gene amplification and mRNA levels, these references still do not establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility.

Applicants argue that even if Bermont fails to provide quantitative data, the reference still supports Applicants' assertion that gene amplification correlates with protein overexpression because it teaches that overexpression of the p185 protein, an indicator of breast cancer, is usually associated with amplification of the encoding gene. The Examiner agrees that Bermont does demonstrate that there is a correlation between overexpression of the p185 protein, however, it may be necessary that the gene encoding the p185 protein be highly amplified amplification in order for the protein to be overexpressed.

On pages 6-8, Applicants discuss the Orntoft reference, in which gene amplification in bladder tumor tissues showed a "striking correspondence" to protein expression levels (page 44). Orntoft examined whether there was correlation between gene amplification and protein overexpression for samples that showed at least a 2-fold change (increase or decrease) in DNA copy number and/or mRNA expression level (Figure 1), and as shown in Table 11 of the Orntoft reference, 9 of the 11 proteins whose expression levels correlated with both mRNA and gene dose changes had transcription alteration levels ranging from 1.6 fold up to 5.7 fold up. Applicants argue that the amount of gene amplification for PR0347 disclosed by Applicants is similar, approximately 2 to 5 fold, and that further, the teachings of Orntoft i.e., that gene amplification correlates with protein overexpression, are not limited to instances where only

aneuploidy is involved. On page 7, Applicants state:

"Rather, Orntoft explains that "(i)n this investigation we have combined genome-wide technology for detecting genomic gains and losses (CGH) with gene expression prosling techniques (microarrays and proteomics) to determine the effect of gene copy number on transcript and protein levels in pairs of non-invasive and invasive human bladder TCCs." Orntoft at 37 (emphasis added). Thus, the correlation between gene copy number, mRNA transcript level, and protein expression level disclosed in Orntoft is not only directly applicable to, but also supports, Applicants' assertion of utility for the PR0347 polypeptide based on the disclosed amplification levels of the nucleic acid sequence encoding PRO347.

Hence, with regard to the Orntoft reference, the Office has not met its burden of establishing that in view of this reference, it is more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility."

Applicants' arguments have been fully considered but are not deemed persuasive. Although Orntoft et al. found a correlation between DNA copy number, mRNA expression and protein level, they looked at a small sample size, and also only at highly abundant proteins, which may have skewed the results. Orntoft et al. themselves discuss that they don't know whether DNA copy number is one of the mechanisms behind the alteration of these eleven proteins, and that larger samples must be analyzed. On page 45, Orntoft et al. state:

"In eleven cases we found a significant correlation between DNA copy number, mRNA expression, and protein level. Four of these proteins were encoded by genes located at a fre-

quently amplified area in chromosome 17q. Whether DNA copy number is one of the mechanisms behind alteration of these eleven proteins is at present unknown and will have to be proved by other methods using a larger number of samples. One factor making such studies complicated is the large extent of protein modification that occurs after translation, requiring immunoidentification and/or mass spectrometry to correctly identify the proteins in the gels."

On page 8 of the response, Applicants discuss the Hu et al. reference of record, and a second Hu et al. reference attached as Appendix 2 (Clinical Cancer Research 2213). The first Hu et al. reference teaches a positive correlation between gene amplification and protein overexpression for *Met* in cancerous tissues, and the second Hu et al. reports that four genes Fra-1, Neogenin, ID-1 and CDC25B, which showed upregulation of cDNA in squamous cell carcinoma compared to normal tissue, also showed that the corresponding proteins were overexpressed in a majority of carcinoma samples compared to normal tissue. Applicants submit that in view of the teachings of both Hu references, one of ordinary skill in the art would not doubt Applicants' assertion of utility. On page 9 of the response, Applicants assert that the Haynes and Gygi references cited in the Office Action do not outweigh the teachings of the above-discussed references, and the teachings of Pollack, Hyman, Varis, Bermont, Orntoft and Hu are more relevant (human cancerous tissues as opposed to yeast). Also argued is that although the Chen reference of record examines correlation between gene amplification and protein overexpression in human lung adenocarcinomas, the teachings of Chen by themselves do not make it more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility. Applicants also argue that this is particularly true when the Chen reference is considered with the totality of the evidence. Applicants state:

"Indeed, although Chen "suggests that it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples," Chen does disclose that in 17% of the samples examined, there was a positive correlation between mRNA abundance and protein overexpression."

Applicants assert that based on the totality of the evidence, one of ordinary skill in the art would believe it to be more likely than not that the PRO347 polypeptide is overexpressed in lung and colon cancer tissues.

Applicants' arguments have been fully considered but are not deemed persuasive. Applicants have argued the supporting references alone and in combination. The Examiner agrees that it is the total body of relevant literature that should be considered in determining the assertion of utility of the polypeptides. The references Applicants use to support their position report on single genes or small sample sizes. Haynes, Gygi and Chen used much larger sample sizes, and additionally, Chen reports that 83% of the samples do not show a positive correlation. An additional reference that teaches that there is not a positive correlation between transcript level and protein level is Anderson et al., Electrophoresis, Vol. 18, pages 533-537, 1997, who found that there was a poor correlation (0.48) between mRNA and protein levels in liver cells (abstract, page 535). They suggest that the two major phases of gene expression regulation (transcription through message degradation on the one hand, and translation through protein degradation on the other) are of approximately equal importance in determining the net output of proteins (page 536, left column). Anderson et al. also reanalyzed the set of data for plasma proteins secreted by the liver that was published by Kawamoto et al., (Gene, 1996, Vol. 16, pages 1977-1981), in which the mRNA-to-protein relationship for nine plasma proteins was

0.96. However, when albumin (which is well-separated from the cluster of the remaining eight and thus exercises a disproportionate influence on the correlation coefficient) was omitted from the calculation, the correlation coefficient is reduced to –0.19, which suggests a very poor correlation (page 536, right column).

On page 10, Applicants state:

"Significantly, a 35 U.S.C. § 101 rejection should only be sustained where the asserted utility violates a scientific principle or is wholly inconsistent with contemporary knowledge in the art. In re Gazave, 379 F.2d 973, 978 (CCPA 1967)." This is addressed in MPEP 2107.02, section III, B, last paragraph, which encompasses credibility of an asserted utility. However, the Examiner does not dispute that the asserted utility is credible. The issue is that the assertion that the polypeptide can be used diagnostically is not considered a substantial utility.

The evidence as a whole clearly indicates that one skilled in the art would not assume that an increase in gene copy number would correspond with an increase in mRNA levels or protein levels without doing the empirical experimentation necessary to measure mRNA and protein levels. The requirement for such empirical experimentation indicates that the asserted utility for the claimed polypeptides is not substantial; it is not in currently available form.

It is believed that all pertinent arguments have been answered.

Conclusion

4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PATENT EXAMINER